START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection

Open Forum Infectious Diseases

REVIEW ARTICLE

START or SMART? Timing of Antiretroviral Therapy Initiation and Cardiovascular Risk for People With Human Immunodeficiency Virus Infection

Mark J. Siedner

Division of Infectious Diseases, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston

The Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection (START) study has reinforced the benefits of early initiation of antiretroviral therapy (ART). However, a notable secondary finding from that study was that immediate initiation of ART did not prevent cardiovascular disease (CVD) events (0.17 vs 0.20 events/1000 person-years, $P = .65$). This result appears to contradict a body of evidence, most notably from the Strategies for Management of Antiretroviral Therapy (SMART) study, which reported a 70% increased hazard of cardiovascular events for those deferring or interrupting treatment. Thus, an important unresolved question is whether the timing of ART impacts CVD risk. In this review, published data on relationships between timing of ART and CVD risk are reviewed. The data support a role for ART in mitigating CVD risk at lower CD4 counts, but data also suggests that, among those initiating therapy early, ART alone appears to suboptimally mitigate CVD risk. Additional interventions to address CVD risk among human immunodeficiency virus-infected populations are likely to be needed.

Keywords. antiretroviral therapy; cardiovascular disease; epidemiology; HIV/AIDS; systematic review.

Two recent landmark studies have lent strong support to a health benefit of early initiation of antiretroviral therapy (ART) for asymptomatic human immunodeficiency virus (HIV)-infected patients with high CD4 counts. Both the Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa (TEMPRANO) and the Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection (START) studies reported reductions of over 40% in the risk of death or an acquired immune deficiency syndrome (AIDS)-defining event when ART was initiated immediately instead of waiting until CD4 thresholds were met (<350 cells/μL in the START study, or the contemporary World Health Organization-based guidelines in the TEMPRANO study) [1,2]. Both studies demonstrated decreased risk of opportunistic infections and appreciable, albeit nonsignificant, reductions in all-cause mortality. However, an unexpected result from the START study was the rate of cardiovascular disease (CVD) events, which did not differ between immediate initiators and those deferring therapy (adjusted hazard ratio, 0.84; 95% confidence interval [CI], .39–1.81; $P = .65$). The TEMPRANO study, which was not designed to capture cardiovascular events, did not report a similar subanalysis.

The finding that early ART for asymptomatic HIV-infected individuals did not prevent CVD complications seems to contradict a body of evidence relating HIV infection to CVD risk. Most notably, a landmark study comparing CD4-count-guided treatment interruptions with continuous ART (Strategies for Management of Antiretroviral Therapy [SMART] study) demonstrated an approximate 70% increase in CVD events in those taking treatment interruptions. Resolving the benefit of ART timing and its impact on CVD risk is a critical question for the field of clinical HIV care. If the benefits are significant, then prioritizing early diagnosis and linkage to ART might provide significant CVD health benefits. If the benefits are not significant, then the search for alternate interventions in addition to ART to mitigate CVD risk in this population will be crucial. This review aims to summarize the evidence about relationships between timing of ART initiation and CVD risk, using nadir CD4 count as a surrogate marker of duration of HIV infection, and with a particular focus on the impact of early ART on prevention of CVD events.

THE SMART STUDY, TREATMENT INTERRUPTIONS, AND CARDIOVASCULAR DISEASE RISK

Soon after it was discovered that combination ART profoundly improved survival for patients with AIDS [3, 4], it became evident that HIV-infected patients were at higher risk than the general population of non-AIDS-related conditions [5–8]. Cardiovascular disease, and particularly myocardial infarction and stroke, were among the greatest non-AIDS risks, and

Received 11 January 2016; accepted 4 February 2016.

Correspondence: M. J. Siedner, Harvard Medical School, Massachusetts General Hospital Center for Global Health, 125 Nashua Street, Suite 722, Boston, MA 02114 (msiedner@mgh.harvard.edu).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofw032

ART rather than HIV infection was thought to be the primary culprit [5, 9, 10]. Concerns about avoiding the toxicity of chronic ART in part spurred a change in the US HIV treatment guidelines to downgrade recommendations to initiate ART for those with a CD4 of 200–350 from "recommended" to "optional" during the period 2001–2006 [11]; and a large randomized controlled trial was conducted to evaluate whether discontinuing ART decreased non-AIDS-related HIV complications. The SMART study randomized approximately 5000 patients infected with HIV on stable ART with a CD4 count above 350 to continuing ART, versus mandated treatment interruptions until CD4 counts dropped below 250, at which point ART was reinitiated [12].

Arguably the most informative result to come from the SMART study was not that treatment interruptions increased the risk of opportunistic infections or mortality, but that patients taking interruptions from ART had an approximately 70% increased risk of cardiovascular complications; moreover, major cardiovascular events occurred 5 times more often than opportunistic infections in those with treatment interruptions (Table 1). The SMART study suggested that, whereas specific ART drugs or drug classes might be associated with a relative CVD risk versus others [13, 14], CVD risk is largely mediated by the effects of untreated HIV infection.

Although the primary SMART study analysis did not differentiate between ART interruptions and timing of ART initiation, in a subsequent analysis, the investigators specifically considered a clinical benefit of earlier ART initiation. When limiting their analysis to the 488 study participants who were ART naive or off therapy for a minimum of 6 months before study enrollment, investigators found a 7 times increased hazard of a cardiovascular event or non-AIDS illness in those initiating therapy at <250 vs >350 cells/μL [15]. As the only study randomizing patients to early versus deferred ART initiation with measured CVD outcomes at the time, this study subanalysis offered the strongest clinical evidence for a preventive role for earlier ART initiation.

Since then, an elegant body of basic and translational research has provided a strong pathophysiologic rationale for a causative role for HIV infection on CVD risk [16]. A combination of immune activation due to HIV and coinfections [17–19], direct HIV infection of vasculature smooth muscle [20, 21], and profound and irreversible depletion of gut T-lymphocytes with resulting microbial translocation [22–24] are thought to combine to precipitate a chronic inflammatory state. Reactive T-lymphocytes and macrophages [25, 26] have been correlated with both CVD outcomes and all-cause mortality [27–30]. Indeed, recent data suggest that as mortality for HIV-infected individuals has decreased from AIDS-defining illnesses, CVD has become the second most common cause of death, after cancer, among those with an undetectable viral load [31]. However, although basic science supports the role of HIV-mediated inflammation as a causative agent in CVD risk, clinical data are crucial to translating this theory into improvements for patient care.

Table 1. Outcomes Reported in the SMART Study [12]

Outcome	Relative Risk for Treatment Interruption	Total Events
Death	1.8 (1.2–2.9)	85
Serious OI	6.6 (1.5–29)	15
Major CV Event	**1.7 (1.1–2.5)**	**104**

Abbreviations: CV,cardiovascular; OI,opportunistic infection; SMART,Strategies for Management of Antiretroviral Therapy.

ANTIRETROVIRAL THERAPY TIMING AND PRECLINICAL ATHEROSCLEROSIS

A host of nonrandomized studies have investigated the relationship between nadir CD4 count and risk of preclinical atherosclerosis, without convincing evidence for a relationship between disease stage at ART initiation and CVD risk (Table 2). It is notable that although multiple studies have reported a relationship between HIV infection itself and carotid intima media thickness (cIMT) [55], only 1 has demonstrated an inverse relationship between nadir CD4 count and cIMT (such that a lower nadir CD4 count is associated with a greater mean cIMT) [32]. In addition, although Hsue et al [43] reported a relationship between lower CD4 count and cIMT progression over time (Table 2), a large prospective study of over 1000 individuals infected with HIV has since reported a counterintuitive direct relationship (such that higher nadir CD4 count was associated with increased progression) [46]. These differential estimates might partially be explained by cohort characteristics. For example, patients in the Hsue et al [43] study had relatively low median nadir CD4 (approximately 200 vs 500 cells/μL), contained a higher proportion of males, and were more likely to be current smokers and have hypertension.

Although less commonly evaluated than cIMT, the presence of carotid plaques has been better associated with nadir CD4 count (Table 2). Investigators of the Multi-Centre AIDS Cohort Study and Women's Interagency Health Study (MACS/WIHS) have reported greater carotid plaque volume with decreasing nadir CD4 count [33, 46]. This causal relationship is strengthened by the presence of a dose-response relationship correlating lower nadir CD4 count with increased prevalence and incidence of carotid plaque.

More recently, several studies have reported strong associations between HIV infection and presence of preclinical coronary artery disease and aortic wall inflammation (Table 2). The largest of these, also from the MACS/WIHS collaboration, reported a 20% decreased odds of coronary stenosis (>50%) for each increase in nadir CD4 count of 100 cells/μL [53]. However, similar to carotid atherosclerosis, the majority of similar studies have not found significant relationships between nadir CD4 count and preclinical disease (Table 2). It is notable that

Table 2. Summary of Studies Reporting Relationships Between Nadir CD4 Count and Preclinical Atherosclerosis

Study	Year	Study Design	HIV-Infected Sample Size	Cohort Median Nadir CD4 Count	Relationship Between CD4 Nadir and Atherosclerosis Risk	Main Findings
Current Carotid Intima Media Thickness						
Jerico et al [32]	2006	Cross-Sectional	132	250	Inverse	Increased odds of cIMT >0.8 mm with a nadir CD4 count <200 vs ≥200 cells/µL (OR, 2.9; 95% CI, 1.4–5.9)
Kaplan et al [33]	2008	Cross-sectional	1931	~450[a]	None	No association between nadir CD4 count and mean cIMT in men (estimate not reported)
Ross et al [34]	2009	Cross-sectional	73	161 (0–868)	None	No association between nadir CD4 count and cIMT ($\beta < 0.01$, $P = .88$)
van Vonderen et al [35]	2009	Cross-sectional	77	~184[a]	None	No association between cIMT and nadir CD4 count (estimate not reported)
Merlini et al [36]	2012	Cross-sectional	163	210 (99–326)	None	No difference in nadir CD4 count between those with normal cIMT (≤1 cm), those with increased cIMT (1.0–1.5 cm), and those with carotid plaque (cIMT > 1.5 cm), ($P = .74$)
Longenecker et al [37]	2013	Cross-sectional	78	NR	None	No association between nadir CD4 count and mean cIMT ($P = .80$)
Desvarieux et al [38]	2013	Cross-sectional	100	~345[a]	None	No difference in adjusted mean cIMT between ART-naive and on ART (4 y) participants Increase in adjusted mean cIMT between those with HIV more than vs <8 years (0.760 vs 0.731, $P = .02$)
Ssinabulya et al [39]	2014	Cross-sectional	245	124 (42–195)	None	No difference in nadir CD4 count between those with elevated cIMT (≥0.78) and those with normal cIMT
Boyd et al [40]	2014	Cross-sectional	47	~222[a]	None	Nonsignificant association between cIMT and nadir CD4 count ($\beta = -0.001$, $P = .9$)
Siedner et al [41]	2015	Cross-sectional	105	122 (80–175)	Direct	Increase mean cIMT with each increase in nadir CD4 count of 50 cells/µL (0.014 mm, $P = .02$)
Pacheco et al [42]	2015	Cross-sectional	591	213 (90–314)	None	Mean nadir CD4 count 215 in lowest tertile of cIMT vs 178 in highest tertile of cIMT ($P = .054$)
Progression of Carotid Intima Media Thickness						
Hsue et al [43]	2004	Prospective cohort	148	106	Inverse	Increased rate of progression of cIMT for participants with a nadir CD4 < 200 (0.0043 mm/year, $P = .08$)
Currier et al [44]	2007	Prospective cohort	134	NR (~35% with nadir CD4 < 200)	Direct	Decreased odds of rapid progression of cIMT (defined as 1 SD, ie, 0.0122 mm/year) for participants with a nadir CD4 count <200 (AOR, 0.10; $P = .04$)
Volpe et al [45]	2013	Prospective Cohort	345	161 (70–276)	Direct	Decreased rate of cIMT progression for each decrease in 100 cells/µL nadir CD4 count (−0.005 mm/year; SD, 0.002)
Hanna et al [46]	2015	Prospective Cohort	1277	~483[a]	None	No association between CD4 nadir and progression of cIMT thickness (RR compared <200 cells vs >500 cells/µL 1.13, 95% CI, .56–2.29, $P = .73$).
Stein [47]	2015	Randomized clinical trial	328	349 (203–455)	None	No association between pretreatment CD4% and cIMT progression ($\beta = -0.07$, $P = .28$)
Current Carotid Artery Plaque						
Kaplan et al [33]	2008	Cross-sectional	1931	~450[a]	Inverse	Increased adjusted risk of carotid plaque with lower nadir CD4 count (vs HIV-uninfected as reference group): CD4 nadir > 500: RR 0.88 (women), 1.24 (men), $P > .18$ CD4 nadir <200: RR 2.00 (women), 1.74 (men), $P \leq .05$
Incident Carotid Plaque						
Hanna [46]	2015	Prospective Cohort	1277	~483[a]	Inverse	Increased adjusted risk of incident carotid plaque with lower nadir CD4 count (vs HIV-uninfected as reference group): CD4 nadir >500: RR 1.28, 0.85–1.94, $P = .23$ CD4 nadir 350–500: RR 1.65, 1.03–2.64, $P = .039$ CD4 nadir 300–350: RR 1.96, 1.20–3.21, $P = .007$ CD4 nadir <200: RR 2.57, 1.48–4.46, $P < .001$
Aortic Wall Inflammation (FDG PET)						
Subramanian et al [48]	2012	Cross-sectional	27	99 (50–250)	None	No correlation between nadir CD4 count and aortic wall inflammation
Preclinical Coronary Artery Disease						
Lo et al [49]	2010	Cross-sectional	78	169 (54–263)	None	No correlation between nadir CD4 count and segment of plaque ($P = .49$), plaque volume ($P = .66$), or Agatston calcium score ($P = .83$)

Table 2 continued.

Study	Year	Study Design	HIV-Infected Sample Size	Cohort Median Nadir CD4 Count	Relationship Between CD4 Nadir and Atherosclerosis Risk	Main Findings
Burdo [25]	2011	Cross-sectional	102	202	None	No correlation between nadir CD4 count and noncalcified coronary artery plaque (estimate not reported)
Duarte et al [50]	2012	Cross-sectional	26	269	None	Borderline, nonsignificant increase in noncalcified plaque volume with decreasing nadir CD4 count (r = −0.36, *P* = .07)
Pereyra [51]	2012	Cross-sectional	113	221[a]	None	Nonsignificant increased prevalence of plaque on CT coronary angiogram among elite controllers with high nadir CD4 than chronic HIV cohort (78% vs 60%, *P* = .28)
Zanni [52]	2013	Cross-sectional	102	175 (57–278)	None	No correlation between nadir CD4 count and number of low attenuation coronary artery plaques (*P* = .72)
Post [53]	2014	Cross-sectional	618	244 (133–332)	Inverse	Decreased risk of coronary artery stenosis >50% for each 100 cell/μL increase in nadir CD4 count (AOR 0.80, 0.69–0.94, *P* = .005).
Abd-Elmoniem [54]	2014	Cross-sectional	35	202	None	No association between nadir CD4 count and right coronary artery atherosclerosis as measured by CT angiography (no estimate reported)

Abbreviations: AOR, adjusted odds ratio; ART,antiretroviral therapy; CI, confidence interval;cIMT, carotid intima media thickness; CT,computed tomography;FDG-PET, fluorodeoxyglucose-positron emission tomography; HIV, human immunodeficiency virus; NR, not reported; OR, odds ratio; RR, relative risk; SD, standard deviation.

[a] Median nadir CD4 count approximated from weighted average of subgroups.

many of these studies are potentially unpowered to detect associations between nadir CD4 and CVD risk. Nonetheless, a meta-analysis of studies including data from approximately 1000 individuals infected with HIV found no significant association between nadir CD4 count and either noncalcified plaque (*P* = .45) or coronary artery stenosis (*P* = .87) [56].

ANTIRETROVIRAL THERAPY TIMING AND CARDIOVASCULAR DISEASE OUTCOMES IN COHORT STUDIES

Several large data sets in the United States, including the Veteran's Aging Cohort Study (VACS), Partners Healthcare and the Kaiser Permanente Healthcare system, as well as large or national cohorts from France and Denmark, have enabled estimation of HIV-related CVD risk (Table 3). In general, these cohort studies increase the support for associations between nadir CD4 count and CVD risk. For example, in the Kaiser cohort, CVD incidence declined over calendar time (1999–2011) as population nadir CD4 increased. At the conclusion of their observation period (2010–2011), they found no difference in risk of myocardial infarction between HIV-infected and uninfected populations (relative risk [RR], 1.0; 95% CI, .7–1.4). The authors [67] point out that their data might be confounded by the fact that the proportion of patients receiving therapy for CVD-related conditions also increased during the period. However, if their estimates are unbiased, these data would support findings from the START study, which demonstrates normalization of CVD risk, compared with the general population, as nadir CD4 counts increased. A second study from the Kaiser investigators, which included more than 22 000 individuals infected with HIV, specifically assessed relationships between nadir CD4 and CVD risk and demonstrated a decreased risk of myocardial infarction with each 100 cell/μL increase in nadir CD4 count [61]. A case-control study from France noted a similar relationship [59]. Moreover, although the Partners cohort investigators, the VACS study investigators, and the HIV Outpatient Study investigators demonstrated relationships between most recent CD4 count and risk of incidence myocardial infarction, they did not assess nadir CD4 count in their reports [28, 60], or they found no association between nadir CD4 and CVD events [58]. Finally, of 5 studies that have explored relationships between HIV disease stage and stroke risk, only 1 identified an inverse relationship between CD4 nadir and stroke risk (Table 3), reporting that a nadir CD4 count below 200 cells/μL more than doubled the risk of stroke [62].

ANITRETROVIRAL THERAPY TIMING AND CARDIOVASCULAR DISEASE OUTCOMES IN RANDOMIZED CLINICAL TRIALS: SMART VERSUS START

Although the above body of evidence suggests a possible, if not inconsistent, role for early ART initiation in mitigating CVD risk, these data have a number of important limitations. First, many of the studies are limited to relatively small sample sizes, preventing the ability to detect small contributions of ART timing to CVD risk. Second, most cohort studies are homogenous in important ways, including restricting to gender (eg, VACS and MACS cohorts), and, more importantly, to small distributions in nadir CD4 count, which limits the ability to compare those initiating early ART with those initiating late

Table 3. Summary of Studies Reporting Relationships Between Nadir CD4 Count and Cardiovascular Disease Events

Study	Year	Study Design	HIV-Infected Sample Size	Cohort Median Nadir CD4 Count	Relationship Between CD4 Nadir and Atherosclerosis Risk	Main Findings
Myocardial Infarction						
Obel et al [57]	2007	Retrospective Cohort	3953	182 (74–290)	None or inverse	Absolute increase in risk of myocardial infarction for those with nadir CD4 count ≤200 cells/µL (RR 2.28, 95% CI, 1.63–3.19) vs those with a nadir CD4 count >200 cells/µL (RR 1.80, 95% CI, 1.17–2.78). No interaction term reported.
Friis-Møller et al [5]	2007	Prospective Cohort	23 437	200 (range 1–2580)	None	No association between nadir CD4 count and risk of myocardial infarction (0.98, 95% CI, .95–1.01) for each 50 cells/µL increase
Lichtenstein et al [58]	2010	Retrospective Cohort	2005	197	None	No association between nadir CD4 count and subsequent cardiovascular event (OR 1.34, 95% CI, .64–2.83 for nadir CD4 <350 vs >500)
Lang et al [59]	2012	Case Control	1173	167[a]	Inverse	Increase in risk of myocardial infarction with each $\log_2$ decrease in nadir CD4 count (OR 0.90, 95% CI, .83–.97)
Freiberg et al [60]	2013	Retrospective Cohort	27 350	362	None	No association between baseline CD4 (first record in veterans affairs system) and incident myocardial infarction (no estimate reported)
Silverberg et al [61]	2015	Retrospective Cohort	22 081	Not reported	Inverse	Decrease in risk of myocardial infarction with each 100-cell increase in nadir CD4 account (ARR 0.88, 95% CI .81–.96).
Stroke						
Rasmussen et al [62]	2011	Retrospective Cohort	4495	292[a]	Inverse	Increase in risk of stroke among those not on ART with a nadir CD4 count ≤200 vs >200 cell/µL (ARR 2.26, 95% CI, 1.05–4.86).
Chow et al [63]	2012	Retrospective Cohort	4308	271	None	No association between nadir CD4 count and risk of stroke (0.97, 95% CI, .90–1.05 for each 50 cells/µL).
Vinikoor et al [64]	2013	Retrospective Cohort	2515	235 (69–407)	None	No association between risk of ischemic stroke and nadir CD4 count ≤200 vs >200 cells/µL (RR 1.31, 95% CI, .76–2.26) for nadir CD4 count
Marcus et al [65]	2014	Retrospective Cohort	24 768	Not reported	None	Among the HIV+ group, no association between nadir CD4 count and risk of stroke (RR 0.80, 95% CI, .4–1.6 comparing nadir CD4<200 with ≥500).
Chow et al [66]	2014	Case Control	60	73	None	No association between nadir CD4 count and odds of ischemic stroke (OR 1.05, 95% CI, .81–1.36 per each 100 cells/µL)

Abbreviations: ARR, adjusted relative risk; ART, antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; RR, relative risk.

[a] Median nadir CD4 count approximated from weighted average of subgroups.

ART. Third, and most important, cohort studies are challenged by residual or unmeasured confounding, such that unaccounted factors associated with both nadir CD4 count and CVD risk (eg, access to high-quality primary care services) could alter estimates of the relationship between them. To overcome these limitations, randomization to early or deferred therapy is needed to better estimate relationships between timing of ART and CVD risk.

Both the SMART and START studies addressed this need through randomization of HIV-infected persons to ART or either ART discontinuation (SMART) or deferring ART initiation (START), respectively. As summarized above, the SMART study reported a 70% increased risk of cardiovascular complications for discontinuing therapy, whereas the START study found no increased risk of cardiovascular complications when initiating ART was deferred.

How can we explain the differences between these 2 studies? It is possible that treatment interruptions (as in SMART) have differential effects on CVD risk than delayed therapy among ART-naive individuals (as in START). However, as mentioned above, the SMART investigators identified similar relationships in a substudy limited to those initiating ART [15]. There are other important differences between the 2 study populations, which theoretically could explain differences in relative rates of CVD events. For example, approximately 50% of patients in the SMART study were on a protease inhibitor, compared with only 20% of patients in the START study, and approximately 6% vs 4% were prescribed abacavir, respectively. Although the regimen imbalance might partially explain the relative increased overall risk of CVD events witnessed in the SMART study, it does not explain the difference in risk comparing those on ART with those who are not. In fact, the relationship observed was counterintuitive, because the regimens in use in the SMART study were more likely to be associated with metabolic abnormalities and would thus be predicted to have a relatively decreased effect on CVD prevention than the regimens used in the START study. Other key differences between study

Table 4. Nadir CD4 Count and Cardiovascular Disease Event Incidence in the SMART and START Studies

Study Group	Nadir CD4	Cardiovascular Events	Event Rate
(per 1000 person-years)			
SMART Treatment Interruption Arm	~200	65	1.8
SMART Continued Therapy Arm	250	39	1.1
START Deferred Initiation Arm	~600	14	0.20
START Immediate Initiation Arm	651	12	0.17

Abbreviations: SMART, Strategies for Management of Antiretroviral Therapy; START, Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection.

groups include a higher median age in the SMART study (43 vs 36 years) and slightly higher rates of current smoking (40% vs 32%), but it is unlikely that these relatively modest differences would account for the approximately 7-fold increased risk of CVD events noted in the SMART study.

Another key difference between study groups was the nadir CD4 count. At enrollment, study participants in the START study had a median nadir CD4 count of 651 cells/μL and a known HIV duration of only 1 year. Moreover, mean CD4 count in the deferred therapy never dropped below 600 cells/μL. In contrast, the median nadir CD4 in the SMART study was 250 cells/μL, and over half of participants had over 6 years of HIV infection before enrollment. Those in the drug conservation group spent most of the observation time (73%) with detectable viral loads and with CD4 counts <500 cells/μL. As such, even the deferred therapy group in the START study can be considered to have significantly shorter duration of HIV viremia and duration of time with low CD4 counts compared with those in the SMART continued therapy arm.

An examination of these 2 studies in combination reveals a nonlinear relationship between nadir CD4 count and CVD risk (Table 4), and the results of this review challenges the implication supported by the START study, which, taken in isolation, suggests that early ART does not prevent CVD outcomes. Instead, early and continuous ART for those with advanced disease does appear to be protective against CVD events. However, for those starting ART relatively early (>500 cells/μL), CVD risk is not clearly reduced substantially by the timing of ART initiation. In other words, above some unclear threshold of immune depletion, earlier ART initiation seems to have a diminished role in preventing CVD risk. It is unlikely that future studies will further elucidate this threshold due to the overwhelming evidence in support of early ART described by the START and TEMPRANO studies. As such, for those starting therapy with preserved immune function, further reductions in risk will likely require additional, non-ART-based interventions.

CONCLUSIONS

In summary, the published literature on the timing of ART initiation and CVD risk supports 3 primary conclusions. First, data from the SMART study, in combination with a handful of nonrandomized studies noting relationships between lower nadir CD4 and increased risk of preclinical or clinical CVD [32, 43, 53, 59, 61, 62], suggest that earlier initiation of ART has a protective effect against CVD events. The majority of these studies, including the SMART study, involved those with relatively low nadir CD4 counts (<250 cells/μL), which lends the strongest support for the benefit of ART among those with advanced disease. Notwithstanding recent recommendations to initiate ART independent of immune status, this implication remains of importance for much of the world's HIV-infected population, because most patients continue to initiate ART well below recommended guidelines [68–70]. Second, a recent group of large cohort studies demonstrate associations between a low recent CD4 count (as opposed to nadir CD4 count) and/or current detectable HIV-1 viremia and clinical outcomes [28, 58, 60]. In combination with results of the SMART study, these data support a role for continuous ART among those who have initiated therapy, to prevent HIV-associated chronic inflammation and resulting CVD risk. Third, for patients starting ART above a CD4 count threshold of 500 cells/μL, the START study suggests that earlier ART initiation has marginal benefits in terms of mitigating CVD risk. This realization should foster further consideration of non-ART interventions to decrease CVD risk among HIV-infected populations initiating therapy with preserved immune function [71, 72].

Acknowledgments

Financial support. M. J. S. received funding from the National Institutes of Health (grants K23 MH09916 and R21 HL124712) and the Harvard Center for AIDS Research.

Potential conflicts of interest. All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. The TEMPRANO ANRS 12136 Study GroupDanel C, Moh R, et al. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med **2015**; 373:808–22.
2. INSIGHT START Study Group IS; Lundgren JD, Babiker AG, et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med **2015**; 373:795–807.
3. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med **1997**; 337:725–33.
4. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med **1998**; 338:853–60.
5. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med **2007**; 356:1723–35.
6. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients–association with antiretroviral therapy. Results from the DAD study. AIDS **2003**; 17:1179–93.
7. Saves M, Chene G, Ducimetiere P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. Clin Infect Dis **2003**; 37:292–8.
8. Currier JS, Taylor A, Boyd F, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr **2003**; 33:506–12.

9. Mary-Krause M, Cotte L, Simon A, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS **2003**; 17:2479–86.
10. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet **2002**; 360:1747–8.
11. De Cock KM, El-Sadr WM. When to start ART in Africa–an urgent research priority. N Engl J Med **2013**; 368:886–9.
12. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med **2006**; 355:2283–96.
13. Currier JS, Lundgren JD, Carr A, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation **2008**; 118:e29–35.
14. D:A:D Study GroupSabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet **2008**; 371:1417–26.
15. Strategies for Management of Antiretroviral Therapy (SMART) Study Group; Emery S, Neuhaus JA, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J Infect Dis **2008**; 197:1133–44.
16. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis **2012**; 205:S375–82.
17. Sylwester AW, Mitchell BL, Edgar JB, et al. Broadly targeted human cytomegalovirus-specific CD4+ and CD8+ T cells dominate the memory compartments of exposed subjects. J Exp Med **2005**; 202:673–85.
18. Hunt PW, Brenchley J, Sinclair E, et al. Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis **2008**; 197:126–33.
19. Wilson EM, Singh A, Hullsiek KH, et al. Monocyte-activation phenotypes are associated with biomarkers of inflammation and coagulation in chronic HIV infection. J Infect Dis **2014**; 210:1396–406.
20. Eugenin EA, Morgello S, Klotman ME, et al. Human immunodeficiency virus (HIV) infects human arterial smooth muscle cells in vivo and in vitro: implications for the pathogenesis of HIV-mediated vascular disease. Am J Pathol **2008**; 172:1100–11.
21. Dube MP, Lipshultz SE, Fichtenbaum CJ, et al. Effects of HIV infection and antiretroviral therapy on the heart and vasculature. Circulation **2008**; 118:e36–40.
22. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med **2006**; 12:1365–71.
23. Douek D. HIV disease progression: immune activation, microbes, and a leaky gut. Top HIV Med **2007**; 15:114–7.
24. Hsue PY, Deeks SG, Hunt PW. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis **2012**; 205:S375–82.
25. Burdo TH, Lo J, Abbara S, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis **2011**; 204:1227–36.
26. Hunt PW. HIV and inflammation: mechanisms and consequences. Current HIV/AIDS Rep **2012**; 9:139–47.
27. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med **2008**; 5:e203.
28. Triant VA, Regan S, Lee H, et al. Association of immunologic and virologic factors with myocardial infarction rates in a US healthcare system. J Acquir Immune Defic Syndr **2010**; 55:615–9.
29. Tien PC, Choi AI, Zolopa AR, et al. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. J Acquir Immune Defic Syndr **2010**; 55:316–22.
30. Duprez DA, Neuhaus J, Kuller LH, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One **2012**; 7:e44454.
31. Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. Lancet **2014**; 384:241–8.
32. Jerico C, Knobel H, Calvo N, et al. Subclinical carotid atherosclerosis in HIV-infected patients: role of combination antiretroviral therapy. Stroke **2006**; 37:812–7.
33. Kaplan RC, Kingsley LA, Gange SJ, et al. Low CD4+ T cell count as a major atherosclerosis risk factor in HIV-infected women and men. AIDS **2008**; 22:1615–24.
34. Ross AC, Rizk N, O'Riordan MA, et al. Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy. Clin Infect Dis **2009**; 49:1119–27.
35. van Vonderen MG, Smulders YM, Stehouwer CD, et al. Carotid intima-media thickness and arterial stiffness in HIV-infected patients: the role of HIV, antiretroviral therapy, and lipodystrophy. J Acquir Immune Defic Syndr **2009**; 50:153–61.
36. Merlini E, Luzi K, Suardi E, et al. T-cell phenotypes, apoptosis and inflammation in HIV+ patients on virologically effective cART with early atherosclerosis. PLoS One **2012**; 7:e46073.
37. Longenecker CT, Funderburg NT, Jiang Y, et al. Markers of inflammation and CD8 T-cell activation, but not monocyte activation, are associated with subclinical carotid artery disease in HIV-infected individuals. HIV Med **2013**; 14:385–90.
38. Desvarieux M, Boccara F, Meynard JL, et al. Infection duration and inflammatory imbalance are associated with atherosclerotic risk in HIV-infected never-smokers independent of antiretroviral therapy. AIDS **2013**; 27:2603–14.
39. Ssinabulya I, Kayima J, Longenecker C, et al. Subclinical atherosclerosis among HIV-infected adults attending HIV/AIDS care at two large ambulatory HIV clinics in Uganda. PLoS One **2014**; 9:e89537.
40. Boyd A, Meynard JL, Morand-Joubert L, et al. Association of residual plasma viremia and intima-media thickness in antiretroviral-treated patients with controlled human immunodeficiency virus infection. PLoS One **2014**; 9: e113876.
41. Siedner MJ, Kim JH, Nakku RS, et al. Persistent immune activation and carotid atherosclerosis in HIV-infected Ugandans receiving antiretroviral therapy. J Infect Dis **2016**; 213:370–8.
42. Pacheco AG, Grinsztejn B, da Fonseca Mde J, et al. Traditional risk factors are more relevant than HIV-specific ones for carotid intima-media thickness (cIMT) in a Brazilian cohort of HIV-infected patients. PLoS One **2015**; 10: e0117461.
43. Hsue PY, Lo JC, Franklin A, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. Circulation **2004**; 109:1603–8.
44. Currier JS, Kendall MA, Henry WK, et al. Progression of carotid artery intima-media thickening in HIV-infected and uninfected adults. AIDS **2007**; 21:1137–45.
45. Volpe GE, Tang AM, Polak JF, et al. Progression of carotid intima-media thickness and coronary artery calcium over 6 years in an HIV-infected cohort. J Acquir Immune Defic Syndr **2013**; 64:51–7.
46. Hanna DB, Post WS, Deal JA, et al. HIV infection is associated with progression of subclinical carotid atherosclerosis. Clin Infect Dis **2015**; 61:640–50.
47. Stein JH, Ribaudo HJ, Hodis HN, et al. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness. AIDS **2015**; 29:1775–83.
48. Subramanian S, Tawakol A, Burdo TH, et al. Arterial inflammation in patients with HIV. JAMA **2012**; 308:379–86.
49. Lo J, Abbara S, Shturman L, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. AIDS **2010**; 24:243–53.
50. Duarte H, Matta JR, Muldoon N, et al. Non-calcified coronary plaque volume inversely related to CD4(+) T-cell count in HIV infection. Antivir Ther **2012**; 17:763–7.
51. Pereyra F, Lo J, Triant VA, et al. Increased coronary atherosclerosis and immune activation in HIV-1 elite controllers. AIDS **2012**; 26:2409–12.
52. Zanni MV, Abbara S, Lo J, et al. Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. AIDS **2013**; 27:1263–72.
53. Post WS, Budoff M, Kingsley L, et al. Associations between HIV infection and subclinical coronary atherosclerosis. Ann Intern Med **2014**; 160:458–67.
54. Abd-Elmoniem KZ, Unsal AB, Eshera S, et al. Increased coronary vessel wall thickness in HIV-infected young adults. Clin Infect Dis **2014**; 59:1779–86.
55. Stein JH, Currier JS, Hsue PY. Arterial disease in patients with human immunodeficiency virus infection: what has imaging taught us? JACC Cardiovasc Imaging **2014**; 7:515–25.
56. D'Ascenzo F, Cerrato E, Calcagno A, et al. High prevalence at computed coronary tomography of non-calcified plaques in asymptomatic HIV patients treated with HAART: a meta-analysis. Atherosclerosis **2015**; 240:197–204.
57. Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. Clin Infect Dis **2007**; 44:1625–31.
58. Lichtenstein KA, Armon C, Buchacz K, et al. Low CD4+ T cell count is a risk factor for cardiovascular disease events in the HIV outpatient study. Clin Infect Dis **2010**; 51:435–47.
59. Lang S, Mary-Krause M, Simon A, et al. HIV replication and immune status are independent predictors of the risk of myocardial infarction in HIV-infected individuals. Clin Infect Dis **2012**; 55:600–7.
60. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. JAMA Intern Med **2013**; 173:614–22.
61. Silverberg MJ, Leyden WA, Xu L, et al. Immunodeficiency and risk of myocardial infarction among HIV-positive individuals with access to care. J Acquir Immune Defic Syndr **2014**; 65:160–6.
62. Rasmussen LD, Engsig FN, Christensen H, et al. Risk of cerebrovascular events in persons with and without HIV: a Danish nationwide population-based cohort study. AIDS **2011**; 25:1637–46.

63. Chow FC, Regan S, Feske S, et al. Comparison of ischemic stroke incidence in HIV-infected and non-HIV-infected patients in a US health care system. J Acquir Immune Defic Syndr **2012**; 60:351–8.
64. Vinikoor MJ, Napravnik S, Floris-Moore M, et al. Incidence and clinical features of cerebrovascular disease among HIV-infected adults in the Southeastern United States. AIDS Res Hum Retroviruses **2013**; 29: 1068–74.
65. Marcus JL, Leyden WA, Chao CR, et al. HIV infection and incidence of ischemic stroke. AIDS **2014**; 28:1911–9.
66. Chow FC, Bacchetti P, Kim AS, et al. Effect of CD4+ cell count and viral suppression on risk of ischemic stroke in HIV infection. AIDS **2014**; 28: 2573–7.
67. Klein DB, Leyden WA, Xu L, et al. Declining relative risk for myocardial infarction among HIV-positive compared with HIV-negative individuals with access to care. Clin Infect Dis **2015**; 60:1278–80.
68. Hoffman S, Wu Y, Lahuerta M, et al. Advanced disease at enrollment in HIV care in four sub-Saharan African countries: change from 2006 to 2011 and multilevel predictors in 2011. AIDS **2014**; 28:2429–38.
69. Lesko CR, Cole SR, Zinski A, et al. A systematic review and meta-regression of temporal trends in adult CD4(+) cell count at presentation to HIV care, 1992–2011. Clin Infect Dis **2013**; 57:1027–37.
70. Siedner MJ, Ng CK, Bassett IV, et al. Trends in CD4 Count at presentation to care and treatment initiation in sub-Saharan Africa, 2002–2013: a meta-analysis. Clin Infect Dis **2015**; 60:1120–7.
71. Lo J, Lu MT, Ihenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. Lancet HIV **2015**; 2:e52–63.
72. Mitka M. Exploring statins to decrease HIV-related heart disease risk. JAMA **2015**; 314:657–9.